REMARKS

Claims 1-19 were pending in this application. In response to the present Office Action, the Applicants have amended Claims 1 and 17. Upon entry of the present amendment, Claims 1-19 are pending in this application.

I. Rejection under 35 U.S.C. § 112

The Office has rejected the term "preventing arthritis" in Claims 1 and 17 as not being enabled by the specification.

In order to expedite the prosecution of the present application, the Applicants have replaced the term "preventing arthritis" with the phrase "reducing the risk of", as suggested by the Examiner.

The Applicants respectfully submit that the amendments to Claims 1 and 17 overcome the present rejection and request that the rejection to Claims 1 and 17 be withdrawn.

II. Rejection Under 35 U.S.C. § 102

The Office has maintained the rejection of claims 1-2 and 4 under 35 U.S.C § 102 as being anticipated by Mynott et al. The Office alleges that Mynott et al. teaches that bromelain, a MEK inhibitor, is useful in a method of treating rheumatoid arthritis.

The Applicants respectfully submit that there appears to be a misunderstanding between the Applicants and the Office regarding the "MEK inhibitors" of the present invention and the alleged "MEK inhibitor" of the Mynott et al reference.

As such, the Applicants respectfully maintain that there is no basis in the Mynott et al. reference for characterizing bromelain as a MEK inhibitor. Furthermore, even if bromelain is a MEK inhibitor, the reference does not teach that bromelain is useful in the treatment of rheumatoid arthritis.

Mynott et al. teaches that bromelain is completely non-specific with respect to its effect on cell function. Bromelain is a crude mixture of proteolytic enzymes, phosphatases and peroxidase, and would therefore affect all cellular functions and signal transduction pathways equally. There is no justification for labeling this crude mixture a "MEK inhibitor." While bromelain may indeed affect the MEK-ERK MAPK pathway, this pathway is one of dozens of *known* signal transduction pathways, each of which would be equally affected by bromelain treatment. To pick the MEK pathway to analyze, in an effort to suggest a role for bromelain's mechanism of action, is a completely arbitrary exercise.

Even if bromelain can be properly characterized as a MEK inhibitor, the reference teaches away from the use of bromelain in the treatment of rheumatoid arthritis. Contrary to the disclosure in the introduction of Mynott et al., bromelain exhibits activity on cell function which would clearly steer one of skill in the art *away* from considerations of treating inflammatory or proliferative disorders with this substance. Although cytokine levels are reduced in the presence of bromelain when *non-specific* (i.e., physiologically irrelevant stimuli are used, like PMA), following relevant stimulation via cell surface receptors, as would occur *in vivo*, cytokine levels are *increased*. This is exactly the opposite of the desired effect. Also, and more importantly, both T cell proliferation *and* B cell antibody production are *increased* in the presence of bromelain. Both of these results are completely contrary to the desired effects of an anti-inflammatory or antiproliferative agent.

As such, the data presented in Mynott et al. would clearly suggest that MAPK inhibition would have a detrimental, rather than beneficial effect, in treating chronic inflammatory or hyperproliferative diseases. Such data would not suggest to the skilled artisan that a MEK inhibitor would be useful in the treatment of rheumatoid arthritis.

Based on the foregoing, the Applicants respectfully submit that Mynott et al. does not anticipate claims 1-2 and 4, and respectfully request that the rejection be withdrawn.

III. Rejections under 35 U.S.C § 103

The Office has maintained the rejection of Claims 1-16 and rejected Claims 17-19 under 35 U.S.C. 103(a) as being unpatentable over Miyazawa et al., Jackson et al., Henry et al., and McGilvray in view of Bridges.

The Office has stated that Miyazawa et al. teaches that MEK is critically involved in interleukin-6 synthesis by Human fibroblast-like synoviocytes. Miyazawa et al. also teaches that a MEK inhibitor can block the activation of MEK and suppression of interleukin-6 production and TNF-α. It also teaches that antagonizing interleukin-6 and TNF would be effective in treating rheumatoid arthritis. Finally, the Office argues that Miyazawa et al. suggests that MEK inhibitors would be beneficial as rheumatoid therapy.

The Office has stated that Jackson et al. teaches inhibition of MEK by a specific MEK inhibitor, SB220025, reducing both interleukin-1β and TNK expression, and being useful in a method of treating chronic inflammation.

The Office has stated that Henry et al. teaches that pro-inflammatory cytokines such as TNF-α and interleukin-1β play important roles in inflammatory diseases such as rheumatoid arthritis.

The Office has stated that McGilvray et al. teaches the involvement of the MAP kinase (MEK) pathway in the activation of monocytic cells during transmigration to inflammatory sites. Specifically, McGilvray et al. teaches the selective inhibition of MAP kinase by the MEK-1 inhibitor PD098059, being useful for blocking and interrupting the adhesion and recruitment of human monocytes and thereby modulating the inflammatory response.

In setting forth the combination rejection, the Office acknowledges that Miyazawa et al., Jackson et al., Henry et al. and McGilvray do not specifically teach the active compounds claimed by the Applicant to be MEK inhibitors useful for the treatment or arthritis, but argues that it would have been obvious to one of ordinary skill in the art in view of Bridges et al., since

the inhibition of MEK is known to 1) suppress the expression and release of pro-inflammatory cytokines such as interleukin-1β, interleukin-6 and TNF-α; and 2) block and interrupt the adhesion of monocytes to the inflammatory sites.

The Applicants acknowledge that the Office has alleged that the original ground of rejection was mischaracterized; however, the Applicants note that the Applicants' Amendment of December 18, 2002 discussed the three primary references, Miyazawa et al., Jackson et al., and Henry et al. in view of Bridges et al. and that the final primary reference McGilvray was also discussed in view of Bridges et al. Though the four primary references were presented in two separate discussions, the Applicants respectfully submit that each of the references was discussed in view of Bridges et al. The Applicants maintain that the primary references would not teach, motivate or suggest to one of skill in the art to use any known MEK inhibitor for the treatment of arthritis.

Furthermore, the Applicants submit that the primary references cannot be properly combined because the references provide no motivation for the combination. Additionally, even if the primary references were combined, they do not teach, motivate or suggest to one of skill in the art to use any known MEK inhibitor for the treatment of arthritis for the reasons originally presented and set forth below.

In response to the Office's position that a p38 MAP kinase inhibitor is considered by one of ordinary skill in the art as a MEK inhibitor, the Applicants respectfully submit that there is a misunderstanding between the Applicants and the Office regarding the terminology "MEK inhibitor" as used in the present invention. As set forth below, the Applicants respectfully maintain that a p38 MAP kinase inhibitors is not a "MEK inhibitor" as used in the present invention.

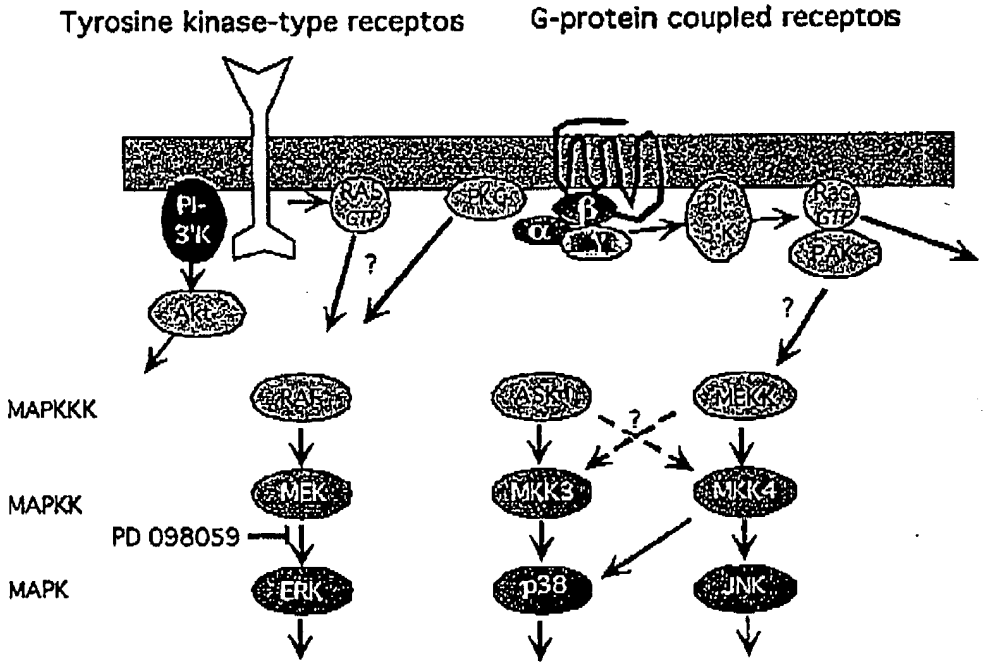
As previously presented, the Applicants respectfully maintain that one of ordinary skill in the art would not have been motivated to employ a MEK inhibitor of the present invention for the treatment of arthritis, including osteoarthritis and rheumatoid arthritis, based on the teaching of Miyazawa et al. Jackson et al., or Henry et al. It would not have been obvious to

one of ordinary skill to use the p38 MAP kinase inhibitors of these three references as MEK inhibitors for the treatment of arthritis as claimed by the Applicants, because p38 MAP kinase inhibitors are distinct from MEK inhibitors. p38 MAP kinase inhibitors are activated by distinct agents and have different substrates and effects than MEK inhibitors. As is explained below, one of skill in the art would recognize that a p38 MAP kinase inhibitor does not act the same as a MEK inhibitor.

The group or family of mitogen-activated protein (MAP) kinases includes three distinct MAP kinase pathways or cascades (FIG. 1, below), serine/threonine kinases ("ERK"), p38 MAP kinases and c-jun N-terminal kinases (JNKs). "The ERK1 and ERK 2 kinases are activated by a cascade of phosphorylation events downstream from the *ras* protooncogene. Initially, Ras interacts with and activates Raf1..., which in turn phosphorylates and activates the dual-specificity kinase MEK1 (MAP kinase kinase or MKK) on two distinct serine residues. Activated MEK1 catalyzes the phosphorylation of $p44^{MAPK}$ (ERK1) and $p42^{MAPK}$ (ERK2) on both a tyrosine and a threonine residue (Thr183 and Tyr 185....)[1]. The MEK inhibitors of the present invention are inhibitors of the upstream kinase MEK of the above-described raf/MEK/erk cascade.

[1] *J. Leopold, et al., "Blockade of the MAP kinase pathway suppresses growth of colon tumors in vivo", Nature Medicine, Vol. 5, No. 7, page 810 (1999)*

Figure 1. Schematic representation of the MAP kinase cascades. Each cascade contains three sequential kinases, a MAP kinase kinase kinase (MAPKKK), MAP kinase kinase (MAPKK) and MAP kinase (MAPK). Each set is activated by small molecular weight G-proteins, such as ras and rac, in an incompletely understood fashion. PD 098059 specifically inhibits activation of the MAPKK, MEK, selectively preventing propagation of a signal through the raf/MEK/erk cascade.



On the otherhand, the compounds investigated in Miyazawa et al., Jackson et al., and Henry et al. are inhibitors of the p38 MAP kinase pathway. SB203580 of Miyazawa et al. is a highly selective inhibitor of p38 MAP kinase, which inhibits the p38 MAP kinase pathway. SB220025 is also a selective inhibitor of p38 MAP kinase. Finally, Henry et al. is directed to potent inhibitors of the MAP kinase p38. The activation of p38 MAP kinase and the c-jun N-terminal kinases (JNKs), alternatively the stress-activated protein kinases, "rel(y) on their phosphorylation at specific dual phosphorylation motifs, namely the sequences Thr-Pro-Tyr (TPY) for JNK and Thr-Glu-Tyr (TGY) for p38 MAP kinase, respectively.... These residues

are specifically phosphorylated by MKK/MEK homologues distinct from MKK/MEKs 1 and 2, that are responsible for the activation of the classical p42/44 MAP kinase isoforms."[2].

In fact, it has been shown that a MEK inhibitor of the present invention, 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide, does not inhibit the phosphorylation of Jun kinase or p38 kinase.[3] As such, it would not be reasonable for one of ordinary skill in the art to utilize results obtained with a p38 MAP kinase inhibitor as motivation for the subject matter of the present invention.

In light of the foregoing, the Applicants respectfully submit that it would not have been obvious to one of ordinary skill in the art that the p38 MAP kinase inhibitors of Miyazawa et al., Jackson et al, or Henry et al. were "MEK inhibitors" as claimed by the Applicants or that the teachings of the three references would suggest that the MEK inhibitors of the present invention would be useful in the treatment of arthritis. As such, the Applicants respectfully request that the rejection of claims 1-19 be withdrawn.

The Office has stated that McGilvray et al. teaches the involvement of the MAP kinase (MEK) pathway in the activation of monocytic cells during transmigration to inflammatory sites. Specifically, McGilvray et al. teaches the selective inhibition of MAP kinase by the MEK-1 inhibitor PD098059, being useful for blocking and interrupting the adhesion and recruitment of human monocytes and thereby modulating the inflammatory response.

The Office acknowledges that McGilvray et al. does not specifically teach the active compound claimed by the Applicant to be MEK inhibitors useful for the treatment or arthritis, but argues that it would have been obvious to one of ordinary skill in the art since the activation of MEK is known to be involved in the inflammatory process, such as by migration and recruitments of monocytes to the inflammatory sites in the body. Furthermore, the inhibition of MEK is known to block and interrupt the adhesion of monocytes to the inflammatory sites.

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[2] *A. Paul, et al., "Stress-activated Protein Kinases: Activation, Regulation and Function", Cellular Signaling, Vol. 9, No. 6, page 404 (1997)*

The Applicants respectfully submit that the teachings of McGilvray et al. would not teach, motivate or suggest to one of skill in the art to use any known MEK inhibitor for the treatment of arthritis. While McGilvray et al. discloses that a MEK inhibitor can effect VLA-4 induced NFkB activation and TF expression in monocytes, this disclosure is in an *in vitro* system with little relevance to *in vivo* inflammatory events. The relevance of VLA-4 mediated adhesion, NFkB activation and TF expression in rheumatoid arthritis is not at all clear, and more relevant endpoints to rheumatoid arthritis (e.g., TNF-alpha) were not assessed. Although monocytes/macrophages are presumed to play an important role in rheumatoid arthritis, they are one of many relevant cell types in this disease. There is little reason to believe that inhibiting monocyte activation alone would have a significant impact on the course of advanced rheumatoid arthritis. It is also presumed by most in the field that significant inhibition of monocyte function would be detrimental with regards to protection from pathogens. The transformed sinovial fibroblast is the proximate culprit in RA, and angiogenesis/endothelial proliferation and T lymphocytes are also though to be important. Strategies which target monocytes as part of their goal, while also affecting fibroblast, endothelial, and lymphocyte activity will likely succeed. Simply demonstrating reduced monocyte activity with a MEK inhibitor following one specific stimulus and assessing less relevant endpoints, such as was done in McGilvray et al., would not lead one of skill in the art to consider arthritis as an indication for treatment.

As such, the Applicants respectfully request reconsideration of the rejection under 35 U.S.C. 103 and request that the rejection of claims 1-19 be withdrawn.

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[3] *J. Leopold, et al., "Blockade of the MAP kinase pathway suppresses growth of colon tumors in vivo", Nature Medicine, Vol. 5, No. 7, page 810-811*

IV. Conclusion

Upon entry of the present amendment, the Applicants submit that this application is now in condition for allowance, which allowance is respectfully solicited.

If the Examiner believes that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at 734-622-2658.

Respectfully submitted,

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